181	retired epidemiologist	USA	7.3 Weighting all the different sources of evidence	7.3 Weighting all the different sources of evidence 1) This implies that epidemiology does contribute (apparently not so much in the past because it's contribution is increasing). Would a complementary sentence be of value, i.e., "Although experimental studies increasingly contribute to establishing causation, an important step is the clear demonstration that experimental exposures are relevant to the human population and the biologic mechanisms in laboratory animals occur in humans." *EFSA Response:* *Consider this comment as: Although experimental studies increasingly contribute to establishing causation, experimental exposures should be relevant to the human population provided that the biologic mechanisms in laboratory animals occur in humans (see also comment #182).*
182	Université de Bordeaux	FRA	7.3 Weighting all the different sources of evidence	• 2187-2189: This implies that epidemiology does contribute (apparently not so much in the past because its contribution is increasing). Would a complementary sentence be of value, i.e., "Although experimental studies increasingly contribute to establishing causation, an important step is the clear demonstration that experimental exposures are relevant to the human population and the biologic mechanisms in laboratory animals occur in humans." *EFSA Response:* *See reply to comment #181.*
183	Centre F Baclesse	FRA	7.4 Biological mechanisms underlying the outcomes	• 2196-2199: While experimental evidence on biologic mechanisms plays a critical role in understanding health impacts from hazards, it is not correct that such information can only be provided by experimental studies. The literature is loaded with examples where this has also been accomplished in epidemiologic studies. What literature is the Panel reading? • 2221-2225: In evaluation of exposure to multiple pesticides, it is valuable to know if these cause toxicity through a common mechanism, but it is not true that this is the only situation where you might want to combine risks. Many human diseases have multiple etiologies that may involve quite different pathways. It is important to evaluate all. The following paragraph describes this quite nicely. *EFSA Response:* *Lines 2196-2199 state: "While many epidemiological studies have shown associations between pesticide exposures and chronic diseases, complementary experimental research is needed to provide mechanistic support and biological plausibility to the human epidemiological observations." The PPR Panel understands that for pesticides, very few (if any) epidemiological studies on pesticides provide mechanistic information.* *On the other hand, lines 2221 state: "The decision to combine risks can be taken if the pesticides share a common mechanism of toxicity". This does not mean that in cases where pesticides have distinct mechanisms of toxicity their risks cannot be combined.*

184	Université de Bordeaux	FRA	7.4 Biological mechanisms underlying the outcomes	• 2196-2199: While experimental evidence on biologic mechanisms plays a critical role in understanding health impacts from hazards, it is not correct that such information can only be provided by experimental studies. The literature is loaded with examples where this has also been accomplished in epidemiologic studies. What literature is the Panel reading? • 2221-2225: In evaluation of exposure to multiple pesticides, it is valuable to know if these cause toxicity through a common mechanism, but it is not true that this is the only situation where you might want to combine risks. Many human diseases have multiple etiologies that may involve quite different pathways. It is important to evaluate all. The following paragraph describes this quite nicely. *EFSA Response:* *Same text as comment #181.*
185	Ministero della Salute	ITA	7.4 Biological mechanisms underlying the outcomes	Page 53 Lines 2221-2224: the issue of mixtures is treated in a very brief way and should deserve some additional considerations. *EFSA Response:* *This is an important point but too premature to be addressed in this Opinion. The terms of reference did not include combined risk of pesticides.*
186	retired epidemiologist	USA	7.4 Biological mechanisms underlying the outcomes	7.4 Biological mechanisms underlying the outcomes 1) While experimental evidence on biologic mechanisms plays a critical role in understanding health impacts from hazards, it is not correct that such information can only be provided by experimental studies. The epidemiological literature is loaded with examples where this has also been accomplished in epidemiologic studies. What literature is the Panel reading? 2) In evaluation of exposure to multiple pesticides, it is valuable to know if these cause toxicity through a common mechanism, but it is not true that this is the only situation where you might want to combine risks. Many human diseases have multiple etiologies that may involve quite different pathways. It is important to evaluate all. The following paragraph describes this quite nicely. *EFSA Response:* *Same text as comments #183 and 184.*
187	Dept. Food Safety, Nutrition, Veterinary Public Health- Istituto Superiore di Sanità	ITA	7.4 Biological mechanisms underlying the outcomes	This section should quote the two previous EFSA opinions on cumulative toxicity of pesticides and pivoting on cumulative risk assessment based on the same phenomenological effects in the same target organ, irrespective of dissimilar chemical structures and toxicity mechanisms Identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile (2013) https://www.efsa.europa.eu/it/efsajournal/pub/3293 Relevance of dissimilar mode of action and its appropriate application for cumulative risk assessment of pesticides residues (2013) http://www.efsa.europa.eu/it/efsajournal/pub/3472 Indeed, these concepts are followed later on in the Recommendations lines 2397-8 and 2425-7

				EFSA Response: *Thank you for your comments. Reference to these two Scientific Opinions has been included in this chapter.*
188	ECPA	BEL	7.4 Biological mechanisms underlying the outcomes	This section should state that sometimes mode of action data indicate a lack of possible effects. If there are biological data that indicate an adverse effect is not likely to occur, this should inform the interpretation of epidemiology studies, particularly considering the limitations associated with epidemiology studies discussed throughout the report. *EFSA Response:* *This is an interesting comment that must be cautiously considered because of the lack of selectivity of pesticides and the existence of secondary targets in humans.* *The following text has been added in line 2220: "Furthermore, sometimes mode of action data may indicate a lack of possible effects. If there are biological data that indicate an adverse effect is not likely to occur in humans, this should inform the interpretation of epidemiology studies. Nevertheless, while primary target site selectivity between pests and humans plays an important role in pesticides safety, secondary targets in mammals must also be considered."*
189	German Federal Institute for Risk Assessment (BfR)	DEU	7.5 Adverse Outcome Pathways (AOPs)	Line 2271, page 54: In this paragraph it is stated that findings that are inconsistent with selected AOPs shall be attributed less weight in the WoE assessment. However, our knowledge on AOPs is not always complete and inconsistent observations need not be less reliable than those in line with the selected AOPs. Perhaps, this limitation should be addressed here. *EFSA Response:* *The PPR Panel agrees that a complete AOP does need to be fully developed for weighting the evidence. However, this paragraph (lines 2271) means that epidemiological findings inconsistent with deep understanding of biological mechanisms (not necessarily with established AOPs) should be given less weight than those finding consistent with AOP or MoA. The rationale behind this assert is the classical Bradford-Hill criteria of biological plausibility* *To clarify this issue, the following text has been added in line 2274: "However, there are relatively few examples of well-documented AOPs and a full AOP/MoA framework is not a requirement for using epidemiology studies in risk assessment."*
190	ECPA	BEL	7.6 Novel tools for identifying biological pathways and mechanisms underlying	Line: 2292: The use of biomarkers in this context will be very difficult. Biomarkers need to be real markers indicative of a single exposure. In the case of transcriptomics, or metabolomics, many substances share a similar initial pattern of transcript/metabolite changes. This is often used as an indicator that a specific pathway is activated. However, activation of a pathway is usually only one element. For example, a large number of compounds, including pesticides, chemicals, pharmaceuticals and natural compounds from plant origin, can activate CAR, PXR or AHR, without leading to hepatic vacuolation or liver tumors. We would suggest adding at the end of the paragraph: "Clear rules for assessing the specificity of biomarkers are necessary".

			toxicity	*EFSA Response:* *Thank you for such suggestion and the sentence "Clear rules for assessing the specificity of biomarkers are necessary" has been added at the end of the paragraph.*
191	German Federal Institute for Risk Assessment (BfR)	DEU	7.7 New data opportunities in epidemiology	Line 2331, page 55: Although data form text messages, credit card purchases or GPS devices may provide valuable information for epidemiological risk and hazard assessment, their use may be immoral or against the law. Therefore, it should be carefully considered beforehand, whether there is a demand for the use of such data for this purpose. *EFSA Response:* *Agree.* *Text in lines 2334-2336 has been amended as the following: "Whereas some of these data sources may provide valuable information for risk assessment, many of them contain personal information that can outpace legal frameworks and arise questions about the ethics of its use for scientific or regulatory purposes. A specific example is constituted by data containing personal information related to health, which are considered sensitive or especially protected, such as electronic medical records, information from occupational or environmental questionnaires, geographic location, health or social security number, etc."*
192	personal	USA	7.7 New data opportunities in epidemiology	Line 2331-2361. I think that we are all excited about the promise of new technologies. However, I think that it is naïve to think that just because something is new and available that it will somehow be useful in the conduct of epidemiologic studies. How does the panel suggest using the content of people's text messages for epidemiologic research? I fail to see how supermarket purchasing data get us closer to assigning a "dose" of pesticides. I can see that you could determine if they purchased produce that "may" have pesticide residues, but do not see how this could be used to improve our exposure assessment, which is a major theme throughout this document. *EFSA Response:* *While this is a preliminary sentence related to the big data opportunities, the Scientific Opinion does not explicitly mention whether supermarket purchasing data or credit card information can be helpful for epidemiological studies. See also comment #191.*
193	Centre F Baclesse	FRA	7.7 New data opportunities in epidemiology	• 2342-2344: Combining data from different systems with health information and agricultural activities can be valuable. This has been done for some time in epidemiology but these data, especially coming from census are not able to provide data at individual level or/and on individual habits like smoking. Use of information from biobanks has also a considerable history. *EFSA Response:* *Agree.* *The following sentence has been added at the end of line 2344: It is acknowledged that in several instances these information were obtained at group level only, and an important challenge will be to obtain data at individual level and/or on individual habits (see also comments #194 and 195).*

194	Université de Bordeaux	FRA	7.7 New data opportunities in epidemiology	• 2342-2344: Combining data from different systems with health information and agricultural activities can be valuable. This has been done for some time in epidemiology but these data especially coming from census are not able to provide data at individual level or/and on individual habits like smoking. Use of information from biobanks has also a considerable history. *EFSA Response:* *See reply to comments #193 and 195.*
195	retired epidemiologist	USA	7.7 New data opportunities in epidemiology	7.7 New data opportunities in epidemiology Combining data from different systems with health information and agricultural activities can be valuable. This has been done for some time in epidemiology. Use of information from biobanks has also a considerable history. *EFSA Response:* *See reply to comments #193 and 194.*
196	ECPA	BEL	8. Overall recommendations	Overall we support most of the recommendations put forward in this section, particularly those aimed at improving future epidemiology studies (e.g. those described in section 8.1). Where possible, we would encourage the PPR Panel to more explicitly indicate how these recommendations should or will be taken forward in practice (i.e. especially those in sections 8.2-8.4). In particular, it would be useful if the PPR Panel provided further explicit guidance on what will be required (i.e. a minimum level of study quality) when using epidemiology evidence in risk assessments for pesticides. *EFSA Response:* *An opinion of the EFSA PPR Panel is often the basis for a guidance document and your comment will be of value in the decision taken as to whether this is appropriate. Thank you for your comment.*
197	retired epidemiologist	USA	8. Overall recommendations	8. Overall recommendations 1) Prospective studies can provide a strong inference for causality. But a prospective study of mortality from diseases that may not be listed on death certificates would not be stronger than a case-control study of such disease identified from hospital or pathologic records. There are many other situations where a prospective cohort study might not be the best choice. Throughout this document the Panel has made many such sweeping statements about epidemiology that are not accurate. Determinations about study quality based simply on the overall study design is dangerous and often wrong. *EFSA Response:* *Recommendation a) 1 (line 2369) encourages the use of prospective studies for pesticide risk assessment as a general rule, but does not make this statement in a sharp way.* *A close reading of this Scientific Opinion shows that table 2 (line 1763) lists a number of study quality considerations for weighting epidemiological observational studies which are not restricted to the study design.* 2) The EFSA document indicates that exposure characterization should avoid "broad exposure classifications such as